Improved diagnosis of cervical spondylotic myelopathy with contact heat evoked potentials

Jutzeler, Catherine R ; Ulrich, Anett ; Huber, Barbara ; Rosner, Jan ; Kramer, John L K ; Curt, Armin

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Abstract

The aim of this study was to reveal the sensitivity and responsiveness of contact heat evoked potentials (CHEPs) to assess cervical spondylotic myelopathy (CSM). A total of 81 patients with clinically and radiologically confirmed spinal cord compression were reviewed. All patients underwent full clinical examinations with combined recordings of segmental CHEPs and somatosensory evoked potentials (dSSEPs) compared to healthy controls. Cross-sectional area, maximal canal compression, and maximal spinal cord compression were determined based on T2-weighted magnetic resonance images (MRI). CHEPs exhibited the highest sensitivity (~95%) to disclose at-level impairments in CSM patients. Normally appearing rostral segments above the level of lesion were impaired in 17% of patients. Comparatively, dSSEPs were less affected (24%) and predominantly impaired at and below the level of CSM. Longitudinal evaluation revealed that CHEPs progressively impaired in parallel with clinical deterioration. CHEPs were sensitive to CSM, revealing evidence of impaired neurophysiology at and below the radiographic level of stenosis. The changes observed above the level of CSM suggest neurophysiological deficits beyond the focally damaged area. Deteriorating CHEPs were observed in a cohort of patients with worsening neurological symptoms, indicating their responsiveness to track CSM. The present study highlights the value of incorporating CHEPs into the diagnosis and prognosis of CSM.

Key Words: Cervical Spondylotic Myelopathy, Contact heat evoked potentials, Prognosis and Diagnosis, Neurophysiological Assessment

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Introduction

Cervical spondylotic myelopathy (CSM) is a common progressive degenerative disorder associated with static or dynamic compression of the spinal cord. In the initial stages of CSM, clinical neurological symptoms are typically mild (e.g., paresthesia), accompanied by minimal functional disability. However, progressive spinal cord compression can cause severe neurologic deterioration in ascending and descending pathways, which in turn leads to major long-term disability.[1-3] Surgical decompression is an effective strategy to ameliorate the neurological and functional consequences of CSM.[4-6] The success of surgery, however, depends on several factors, including early and accurate diagnosis.[7, 8] To evaluate structural abnormalities underlying patient reported symptoms, magnetic resonance imaging (MRI) represents a common diagnostic and prognostic tool.

The difficulty with relying on MRI alone is that a large proportion of otherwise healthy individuals (i.e., asymptomatic) present with some form of spinal cord compression.[9, 10] To complement the radiographic investigation, neurophysiological assessments have been employed to measure the functional integrity of the spinal cord. Most commonly, this involves electrical stimulation of mixed nerves (e.g., ulnar and tibial) or a cutaneous area (so-called “dermatomal”), and the acquisition of somatosensory evoked potentials (SSEPs or dSSEPs, respectively).[3, 11-13] As an objective measure of conduction in the dorsal columns, SSEPs have contributed to better prediction of long-term outcomes following surgery[3].

Recent studies have demonstrated the sensitivity of an alternative neurophysiological technique, so-called contact heat evoked potentials (CHEPs), to detect damage associated with spinal cord disorders. This prominently includes traumatic spinal cord injury and cases of syringomyelia.[14-16] In response to rapid heat stimuli, CHEPs reflect the recruitment of small diameter afferents in the periphery, decussation of second order neurons at (or near) the level of entry, afferent conduction in the spinothalamic tract, and, finally, cortical activation in brain areas involved in nociception.[17] The sensitivity of CHEPs compared to SSEPs is purportedly related

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to physiologically greater axial coverage of the central spinal cord area (gray and white matter), as well as the anterolateral position of the spinothalamic tract.[18] The later may render CHEPs particularly sensitive to detect ischemic insults to the spinal cord arising due to occlusion of the anterior spinal cord artery.[19] Surprisingly, the application of CHEPs in CSM has not been previously examined. Additionally, few studies to date have provided evidence that CHEPs are responsive to longitudinal changes in pathology over time.

The overall aim of this study was to assess the sensitivity of CHEPs to reveal signs of spinal cord impairment in patients suspected to suffer from CSM. We hypothesized, based on greater anatomical coverage and anterolateral position of the spinothalamic tract, that CHEPs would exhibit superior sensitivity compared to a conventional neurophysiological approach (i.e., SSEPs). A secondary aim was to examine changes in CHEPs over time in patients with persistent or worsening neurological conditions. Here we hypothesized that CHEPs would deteriorate over time, corresponding with patient reported symptoms. To address our aims, we reviewed a large number of patients with radiologically and clinically confirmed CSM assessed with CHEPs.

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Material and Methods

Patients

A single-center retrospective study was conducted at the Spinal Cord Injury Center, University Hospital Balgrist in Zurich, Switzerland. The study includes patients with clinical symptoms of CSM that was confirmed by radiographic evidence of spinal cord compression, who were referred to our outpatient clinic between January 2009 and January 2016. Patients with any level (within cervical cord) and varying severity of CSM were included. Any patient with ossification of posterior longitudinal ligament, radiculopathy, diabetes mellitus, and a history of spinal tumor was excluded from the study. In addition, 50 age- and sex-matched healthy individuals were recruited between October 2015 and January 2016 in order for the acquisition of control values. These subjects were specifically examined to determine objective criteria to evaluate CHEPs. Exclusion criteria for the healthy cohort included intake of medication, presence of any neurological disorder, presence of pain, and pregnancy. All healthy individuals and patients provided written informed consent and all procedures described below were in accordance with the Declaration of Helsinki and approved by the local ethics board 'Kantonale Ethikkommission Zürich, KEK' (ref. number: EK-04/2006).

Clinical assessments

Prior to the neurophysiological assessments, all patients were thoroughly examined by a trained physician according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) published by the American Spinal Injury Association (ASIA).[20-23] This examination was applied to determine sensory, motor, and neurological levels of injury, as well as the severity of injury (i.e., completeness). Two aspects of sensation, light touch and pinprick (sharp-dull discrimination), were tested at predefined skin areas for the dermatomes C3-Th1 and classified on a scale of 0-2 (i.e., 0 = absent, 1= impaired, 2=normal). Furthermore, the

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physician assessed the presence of disease-characterizing symptoms including pain or stiffness in the neck, clumsiness in the hands, tingling or numbness in extremities, muscle weaknesses, gait disturbances, as well as bladder and bowel dysfunction.

Neurophysiological assessments

CHEPS and dSSEP were acquired from dermatomes above, at, and below the level of MRI-defined level of CSM with patients in the supine position. For the CHEPs recording, we used the same methodology as the one employed in previous studies.[24, 25]

Dermatomal SSEPs were elicited through repetitive electrical stimulation (repetitive square wave impulse of 0.5-millisecond duration) of the dermatome using self-adhesive bipolar stimulation electrodes and the Keypoint recording device (Medtronic, Minneapolis, MN). Stimulation frequency was set at 3.1 Hz and two traces of 200 stimulations were applied per dermatome. The stimulation intensity was individually set at 5-fold electrical perception threshold. Cortical responses (N1P1) were recorded from the contralateral scalp (C3'-C4' in a 10-20 electrode configuration, referenced to Fz) to the C4, C6, and C8 dermatomes being stimulated using needle electrodes (12 mm; Spes Medica s.r.l., Battipaglia, Italy).[13] Electrode impedance was kept below 5kΩ, which was verified prior to the initiation of each session and all signals were sampled at 10 kHz and bandpass filtered 2 Hz to 2 kHz. Averaged dSSEPs were visually inspected for N1 and P1 latencies.

Neuroimaging: Acquisition and analysis

Spinal MRI of the whole cervical spine was performed in all patients included in the study (3T tesla; Siemens Medical Systems, Erlangen, Germany). CSM was diagnosed in all patients based on the clinical examination in conjunction with T1- and T2-weighted MRI images. CSM was defined as "MRI showing spinal stenosis and cord compression as a result of osteophyte

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overgrowth, disc herniation, or ligamentum hypertrophy" and formally diagnosed by a trained radiologist.[1]

Prior to analysis the MRI data were screened for movement artefacts. From each MRI, the maximum canal compromise (MCC) and maximum spinal cord compression (MSCC) was identified radiologically as previously described.[26, 27] Using the midsagittal slice of T2-weighted images, the anteroposterior canal diameter at the level of maximum compromise (stenosis) was compared with the anteroposterior canal diameter at the normal levels immediately above and below the level of stenosis. To quantify the degree of maximum canal compromise the following ratio was calculated: MCC= canal diameter at stenosis / (canal diameter above + canal diameter below). Similarly, the maximum spinal cord compression (MSCC) was measured (at the same level as maximum canal compromise) and calculated. In case of multi-segmental compression (n=6), the canal diameter of the normal levels was measured immediately above and below the last level of stenosis.

Furthermore, the signal change ratio was determined according Nouri.[28] Briefly, the region of hyperintensity or, if not applicable, from the level of greatest cord compression was compared against an average reference on the spinal cord at C7/T1 and C2 using T2 weighted images. Lastly, the cross-sectional spinal cord area was measured using a well-established semi-automated segmentation method.[29-31] Ten contiguous 2.75 mm axial slices were reformatted using the center of C2/C3 intervertebral disc as a caudal landmark, with the slices perpendicular to the spinal cord. All analyses were performed using JIM 7.0 (Xynapse Systems, Aldwincle, UK).

Control values

Contact heat evoked potentials, pin prick, and light touch testing was unilaterally performed in the dermatomes C4, C6, and C8. For the dSSEPs, controls values were taken from a previous study of our group (see Table 1).[32]

Interpretation of dSSEPs and CHEPs

Averaged dSSEPs were visually inspected for N1 and P1 latencies and classified as having (1) a normal N1 latency (within +2 standard deviations [SD]), (2) a delayed N1 latency (≥+2SD of mean control values), or (3) an absent N1 latency. The interpretation of the CHEPs was based on the visual inspection of the average waveform for N2 and P2 latencies and amplitudes. The classification comprised of five the categories normal (5), low amplitude and normal latency (4), normal amplitude and delayed latency (3), low amplitude and delayed latency (2), and absent CHEPs (1). The control values from healthy subjects served as reference for the classification. Both, N2 latency and N2P2 amplitude, were classified as impaired when the values were lying outside the range of healthy controls.

Statistical analysis

Non-parametric tests were applied to determine significant differences CHEP N2 and P2 latencies, and N2P2 amplitudes between healthy controls and patients with CSM for each dermatome (i.e., C4, C6, and C8). The patient's cohort was divided into two groups, specifically (a) above MRI level of lesion (i.e., dermatome analyzed is above the MRI lesion) and (b) at/below MRI level of lesion (i.e., dermatome analyzed is at or below the MRI lesion).

The sensitivity of CHEPs, dSSEPs, PP, and LT to detect CSM was compared to the conventional diagnosis of CSM, including clinical and imaging assessments (i.e., "golden standard"). To account for unequal number of patients that underwent dSSEP, CHEPs, and clinical testing, only patients who underwent all measurements were included (N=59). The presence of CSM was correctly determined if any of the examined dermatome indicated alterations (i.e., impaired or abolished function). This was done for all measurement techniques

separately. A confidence interval of a proportion analysis was conducted for each dermatome tested and level of CSM lesion (C3 to C6) to identify the proportions of detected CSM-related alterations by means of CHEPs. The classifications of the outcome of CHEPs were dichotomized into the two categories 'normal' and 'impaired/abolished'. Proportions and confidence intervals of total measured dermatome and number of successful detections of CSM (i.e., impaired and abolished) were calculated.

Receiver operating characteristic (ROC) curve analysis was performed to further evaluate the sensitivity and specificity of CHEPs parameters (i.e., N2 latency and N2P2 amplitude) for each dermatome. All healthy controls and CSM patients, independent of their level of lesion, were included in the analysis. In order to include patients with abolished CHEPs in the ROC analysis, an arbitrary value of 600ms was imputed for their N2 latency. This value was chosen, as we did not expect any cortical waveforms beyond 600ms. The amplitude of an abolished waveform was set to 0. The area under the ROC curve (AUC) was calculated as an index marker for the diagnostic accuracy. A diagnostic test is typically considered clinically useful if the AUC value exceeds 0.75.[33]

All statistical analyses were performed using IBM`s Statistical Package for the SocialSciences (SPSS) version 19.0 (Armonk, New York, U.S.). All Bonferroni correction was used to account for multiple comparisons. Statistical significance was set at $\alpha = 0.05$.

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Results

Demographics, clinical assessments, and MRI findings

Out of 91 reviewed patients with CSM, 10 had to be excluded from the statistical analysis due to missing or not interpretable data (e.g., movement artefacts in MRI). The remaining 81 patients were comprised of 52 males and 29 females with a mean age of 53.1 ± 15.2 years (range from 19 to 85 years). All patients were ambulatory (AIS impairment scale D (n = 66) or E (n = 15). Patients classified as AIS E (i.e., normal sensory and motor function according to ISNCSCI) presented with symptoms including pain and/ or stiffness of the neck (n=9), bladder problems (n=10), clumsiness of the hands (n=5), and balance problems (n=3).The level of CSM determined by the MRI ranged from C3 to C8 (C3 (n=12, 14.8%), C4 (n=22, 26.2%), C5 (n=21, 25.9%), C6 (n=23, 28.4%), C7 (n=2, 2.5%), and C8 (n=1, 1.2%)). The healthy control cohort consisted of 35 male and 15 female individuals (mean age 51.8 ± 9.9, range from 19 to 80 years). The characteristics of all individuals (i.e., patients and controls) are summarized in Table 1. In patients, the maximum spinal cord compression (MSCC) was 18.2 ± 12.5% and maximum canal compromise (MCC) 27.9 ± 12.4%, which is comparable to previous findings.[34] In 33 patients a T2 signal hyperintensity with a signal change ratio of 1.25 ± 0.26 was detected. The mean cross-sectional spinal cord area (SCA) at level C2 was 72.1 ± 6.6mm^2 (range 50.5-81.5), which is significantly smaller compared to previously reported values of healthy control cohorts.[31, 34, 35]

Contact heat evoked potentials

In patients, CHEPs were assessed in 484 dermatomes (average number of dermatomes measured =4.8 +/- 1.9). The mean (±standard deviation) pain rating, N2 latency, and N2P2 amplitude of CHEPs from healthy individuals for each dermatome are summarized in Table 2. 54% (n=261) of recordings were within segments above the MRI level of lesion. Reduced N2P2

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amplitudes and delayed N2 latencies were observed for dermatomes located above and at/below the level of lesion compared to the healthy cohort. Independent of lesion level, C4, C6, and C8 CHEPs were impaired or abolished in 41.5% [95% CI: 0.33-0.52], 73.2% [95% CI: 0.64-0.81], and 77.9% [95% CI: 0.69-0.85] of CSM patients, respectively. The breakdown by lesion level is shown in Figure 1.

The ROC analysis revealed high diagnostic accuracy for C4, C6, and C8 CHEPs N2 latency and N2P2 amplitude to discriminate CSM compared to healthy age-matched controls (Figure 2). Area under the curve (AUC) increased from C4 to C8 for both amplitude and latency. The areas under the ROC curve (AUC) for CHEPS N2P2 amplitude and N2 latency tested at C4 dermatome to discriminate CSM vs no CSM were and 0.771 (95% CI, 0.695-0.848, p<0.001), respectively. For C6 and C8 dermatomes, the AUCs for N2P2 amplitude were 0.814 (95% CI, 0.753-0.874, p<0.001) and 0.837 (95% CI, 0.776-0.898), respectively, and N2 latency 0.852 (95% CI, 0.796-0.907, p<0.001) and 0.889 (95% CI, 0.835-0.943), respectively.

Comparison of CHEPs, dSSEP, and clinical testing sensitivity

In patients examined with CHEPs, dSSEPs, and LT/PP (n=59), CHEPs showed the highest sensitivity to detect radiographic evidence of CSM (94.9%, n=56; Figure 3), followed by pinprick (72.9%, n=43), dSSEPs (23.7%, n=14), and light touch (23.7%, n=14).

Follow up measures in CSM

In reviewing the entire CSM cohort, we identified 13 patients who underwent annual follow-up assessments for one or two years post initial diagnosis. The characteristics of these 13 patients (mean age 45.7 ± 12.9 years, 3 female and 10 male) are summarized in Table 3. 10 patients (3 female) experienced deteriorating neurological symptoms associated with CSM, including paraesthesia, hypersensitivity, and pain (n=6), muscle weakness/clumsiness (n=3), gait disturbances (n=3), and bladder problems (n=3). No changes were evident according to MRI

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(MSCC, SCC, and hyperintensity ratio), dSSEPs, LT, or PP. Based on our classification of CHEPs, all 10 patients experiencing worsening symptoms demonstrated objective evidence of deterioration (i.e., increased latency, reduced amplitude) above, at, and/or below the level of injury (Figure 4). In the 3 patients with stable CSM symptoms, CHEPs did not change over time.

Discussion

In the present study, we have provided evidence that CHEPs are highly sensitive to detect spinal cord impairment related to CSM. Impaired CHEPs were evident in those spinal cord segments that corresponded with obvious signs of myelopathy (i.e., at- and below-level), as well as seemingly unaffected rostral segments. Comparatively, the sensitivity of clinical testing (i.e., pin prick and light touch) and dSSEP was limited to spinal segments at or caudal to the radiographic level of stenosis. Longitudinal evaluation of 13 patients found that worsening neurological symptoms (n=10) were accompanied by deteriorating CHEPs (Figure 4). Importantly, deterioration was apparent in dermatomes above, at-, and below the radiographic level of stenosis. Collectively, these observations highlight focal (i.e., at level of stenosis), as well as extended pathology (i.e., rostral and caudal to stenosis) related to CSM and a greater sensitivity to detect CSM using CHEPs.

Sensitivity of CHEPs

Previous studies demonstrate that CHEPs are sensitive to detect a variety of spinal cord impairments, including severe cord damage (i.e. post traumatic cyst and syrinx formation) and spinal cord syndromes (i.e. anterior and central cord syndromes).[14] Their advantage, compared to other neurophysiological techniques (e.g., dSSEPs), is a unique ability to detect pathology in both affected and 'normal appearing' spinal segments (i.e., rostral to the level of injury). Differences in underlying anatomy (somato-topic organization of spinal tracts including

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fiber decussation) and vulnerability to ischemia (central cord area is highly susceptible to impairment of blood supply) may explain, in part, the higher sensitivity of CHEPs to detect CSM (Figure 5A). As a function of small diameter afferents decussating upon entry into the spinal cord, CHEPs are particularly well suited to detect pathology in central gray matter. In contrast, SSEPs enter the spinal cord and project cortically via the dorsal columns without decussation and higher collateral vascularization. Consequently, SSEPs only reflect pathology in dorsal and dorsolateral regions of the spinal cord. CHEPs may also be more sensitive because of the position of the spinothalamic tract relative to the dorsal columns and the tendency for CSM to emerge in the anterior regions of the spinal cord.[36, 37]

Functional and structural changes rostral to the level of lesion

What appears to be most interesting about CHEPs is the detection of impairment in "normally appearing" spinal segments above the level of stenosis. As illustrated in Figure 5B, 17% of examined dermatomes rostral to the level of stenosis, without any obvious sign of impairment, showed altered or even abolished CHEPs. These changes in amplitude and latency may reflect a form of *extended* myelopathy, which occurs secondary to the direct mechanical trauma caused by spinal cord compression (i.e., *focal* myelopathy at the level of CSM, see Figure 5C). Alternatively, emerging evidence suggests that CSM results in changes along the entire neuro-axis (Figure 5D). Since CHEPs are ultimately a reflection of cortical processing, their impairment may also reflect changes in the brain,[38, 39] where cortical reorganization alters the pattern of activity for processing noxious heat stimuli, yielding reductions in amplitude and shifts in latency.

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Responsiveness of CHEPs

While previous studies have demonstrated the utility of CHEPs to detect damage in the spinal cord,[14] none have examined the natural course (in the absence of surgery) over time. In order to better understand the course of in CSM with either stable findings or slow progression, a recent review has pointed out the need for such investigation.[40] The longitudinal analysis of 13 patients demonstrates a very strong association between neurophysiology and symptomology (Figure 4). As illustrated in Figure 4, CHEPs deteriorated progressively, spreading from the level of stenosis to rostral and adjacent spinal segments in 10 patients with worsening neurological symptoms. Indicating high sensitivity and specificity to detect CSM, CHEPs remained stable in the remaining 3 subjects that did not report any change in their neurological condition (Table 3). Compared to these robust changes in CHEPs, conventional MRI (i.e., T1 and T2 weighted images) did not yet track patients' deteriorated neurological symptoms. Although limited by a small sample size (n=10), these observations point to the need for a multi-modal assessment of CSM, coupling MRI with electrophysiology to track meaningful changes in spinal cord function. This may be particularly important in the early stage of CSM, where MRI alone does not yet reveal evidence of pathology (compared to age-matched healthy individuals). Furthermore, based on this knowledge, CHEPs could serve as a useful tool to investigate the efficacy of interventions (surgical or non-surgical) to prevent the progression of CSM.

Limitation and Future Directions

The retrospective nature of the study represents a notable limitation. Of concern, only clinically assumed CSM patients were reviewed, which may have led to a selection bias. A prospectively designed longitudinal study involving a range of patients with and without CSM measured with MRI and CHEPs is warranted to address this limitation. In this retrospective study, the clinical assessment was based on using the ISNCSCI protocol which is an

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international standardized and accepted clinical assessment tool in traumatic spinal cord disorders. Future studies need also to employ the Japanese Orthopedic Association (JOA) score as it represents nowadays the standard to assess the severity of clinical symptoms in non-traumatic CSM patients. The sample size of our longitudinal study is relatively small, which limits statistical power. Nevertheless, it is the first longitudinal study tracking functional changes by means of CHEPs without any surgical intervention. To assess the extent and the specific level of CSM, adjustments to the current CHEPs protocol are needed. Most notably, the analysis of contact heat stimulation will benefit from assessing several cervical levels. Lastly, future studies should consider the effect of surgical (or non-surgical) intervention on CHEPs, in order to determine their responsiveness to treatment and prediction of recovery. In turn, this will improve the decision making process during treatment planning.

Conclusion

The present study highlights the sensitivity and responsiveness of CHEPs in patients with CSM. Corresponding with radiographic evidence, pathological CHEPs were evident at the level of CSM. For the first time, we present data that suggests sub-clinical pathology in rostral "normal" appearing spinal segments. Importantly, these changes were observed to occur over time, progressing from the level of stenosis into adjacent rostral spinal segments. Overall, our observations strongly highlight the potential value of incorporating CHEPs into the diagnosis of CSM.

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Competing financial interests

The authors declare no competing financial interests.

Authors Contributions

Catherine Jutzeler contributed substantially to the conception and design of the study, the data acquisition, analysis, and interpretation. Furthermore, she drafted the research article. Anett Ulrich was involved in the data acquisition and participated in revising the research article. Barbara Huber was involved in the data acquisition and interpretation, as well as revising the research article. Jan Rosner was substantially involved in the data collection, data analysis, and revising the research article. John Kramer contributed substantially to the data analysis and interpretation, and was involved in drafting the research article. Armin Curt made substantial contributions to study conception and design as well as participated in revising the research article critically for important intellectual content.

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Figure Legend:

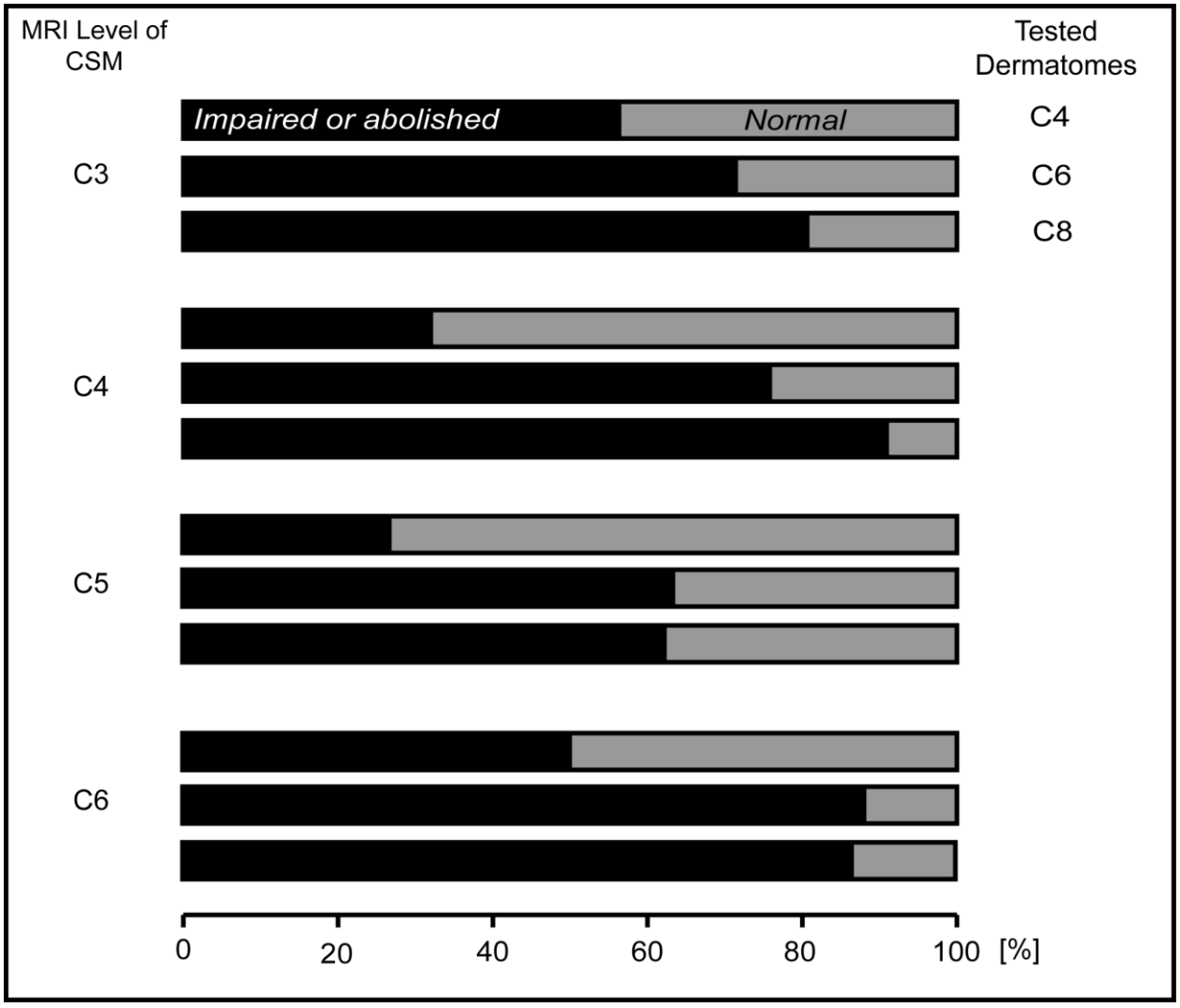

Figure 1: Percentage of pathological CHEPs according to tested dermatomes. Independent of the MRI level of CSM, testing dermatome C8 or C6 yielded the highest proportion of pathological (i.e. impaired or abolished) CHEPs. Conclusively, acquiring CHEPs from C8 or C6 (i.e., likely located below the level of CSM according to MRI) will be most sensitive to indicate spinal cord impairment in CSM.

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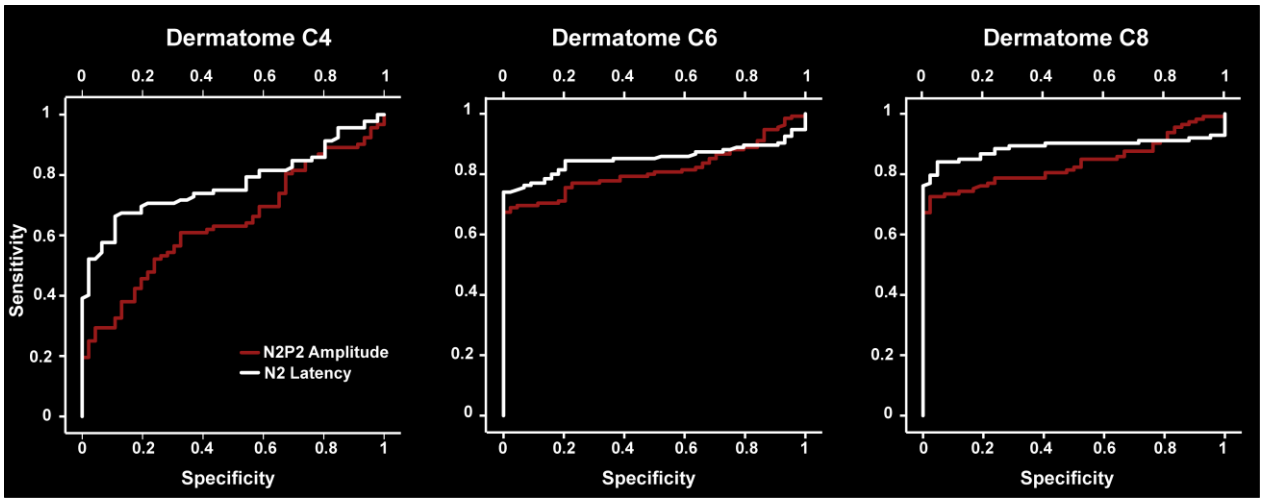

Figure 2: ROC Curve analysis for N2 latency and N2P2 amplitude measured in dermatome C4, C6, and C8. Both, N2 latency and N2P2 amplitude showed high diagnostic accuracy to discriminate CSM vs no CSM. As expected, the lowest AUC (0.641) was found for both measures acquired from dermatome C4 as also patients with CSM level below C4 (i.e., C4 dermatome was arguably unaffected) were included in the analysis.

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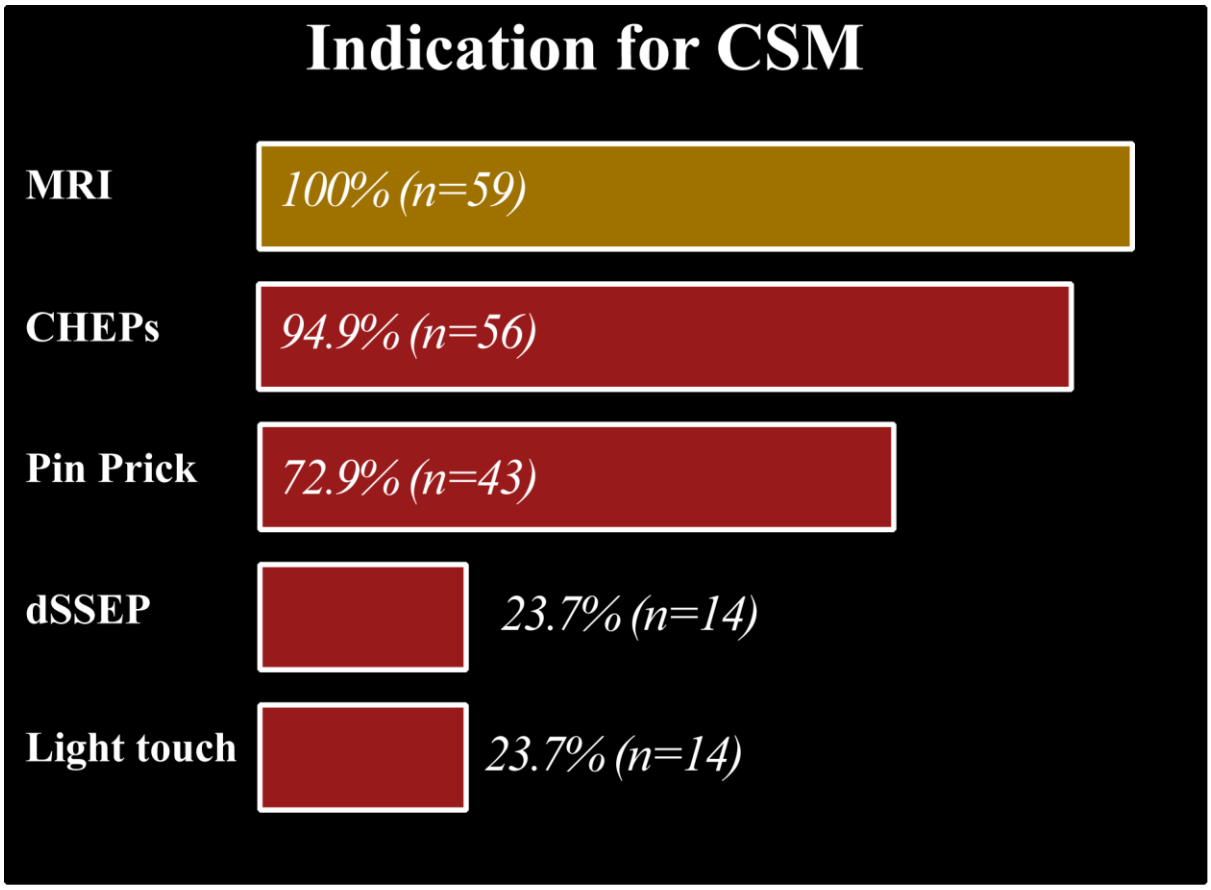

Figure 3: Sensitivity of clinical sensory testing, contact heat evoked potentials, and dermatomal SSEPs in CSM. In all enrolled patients, there was radiological evidence (i.e. signs of cord compression) for an existing CSM. Overall, CHEPs showed the highest sensitivity to detect CSM in comparison to dermatomal SSEPs (dSSEP), pin prick, and light touch testing. The bars represent the percentage of patients with at least one impaired dermatome above, at, or below the level of CSM measured by means of CHEPs, dSSEP, pinprick, or light touch.

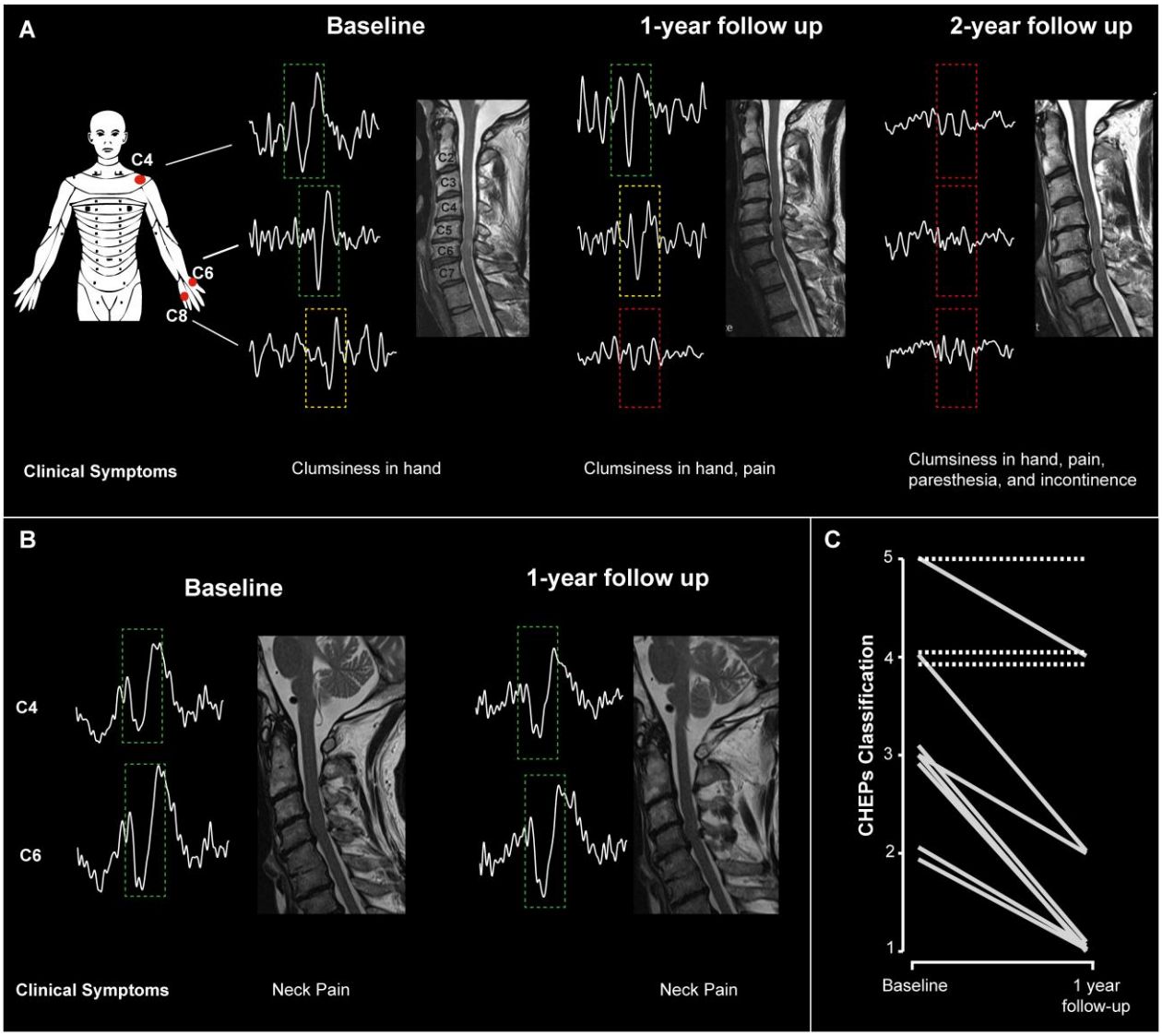

Figure 4: Responsiveness of CHEPs. (A) At the initial examination (baseline) this CSM patient showed first signs of impairment (i.e., reduced amplitude and delayed latency) in CHEPs in dermatome C8, while C4 and C6 were still normal. In one year time with increasing clinical symptoms, CHEPs in C8 became abolished and altered in C6 (i.e., reduced amplitude and delayed latency), while remained normal in C4. At the 2-year follow up with seriously worsened clinical condition CHEPs of all dermatomes were abolished. The changes in CHEPS are in line with the aggravation of clinical symptoms. (B) This patient had no change in the clinical symptoms and radiological evidence over time and CHEPs remained unchanged. (C) Summary figure of changes in CHEPs classification over time in 13 CSM patients. Three patients had no changes in clinical symptoms and no change in CHEPs (dotted lines). The remaining 10 experienced aggravation of their clinical symptoms and a decline in the CHEPs classification (characteristics of the patients are summarized in Table e-2.

Green: Normal CHEP (i.e., normal amplitude and normal latency)
Yellow: Impaired CHEPs (i.e., reduced amplitude and delayed latency)
Red: Abolished CHEP

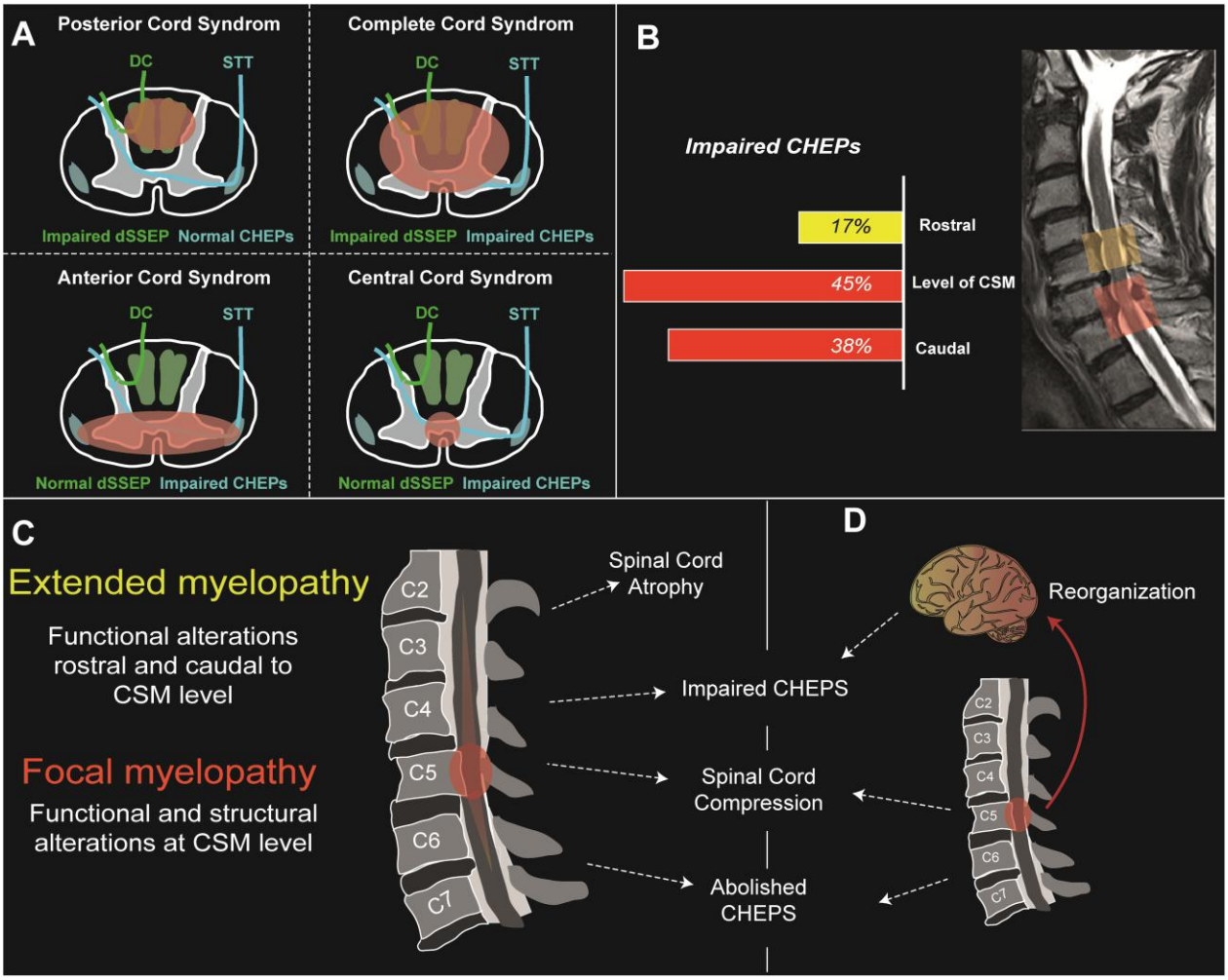

Figure 5: (A) The somato-topical organization of dorsal column tracts and spino-thalamic pathways underlay the specific sensitivity of CHEPs in central cord pathology superior to SSEP. (B) CSM is defined by incomplete central cord damage and impaired CHEPs can be revealed rostral, at, and below the level of CSM. (C) Spinal cord compression leads to damage expanding from the primary focal level of compression in both the rostral and caudal directions into adjacent spinal segments. In contrast to conventional MRI or clinical testing, advanced MRI techniques (spinal cord area, cord compression measures) and neurophysiological assessments (i.e., CHEPs) allow the detection of the damage in rostral spinal segments. (D) Despite originating spinally, the consequences of CSM are evident along the entire neuro-axis (i.e., spinal cord and brain). As such, cerebral reorganization might be involved in the impairment of CHEPs above the level of lesion.

Table 1. Demographic and clinical details of the study cohorts

Parameter	Groups	
	Healthy controls	CSM Patients
Gender [male : female]	35:15	52 : 29
Age [yrs]	51.8 ± 9.9	53.1 ± 15.2
Height [cm]	172.3 ± 18.4	171.8 ± 13.9
ASIA Score (D:E)*	0:50	66 : 15
Duration of CSM [yrs]		2.4 ± 3.0
MRI level of injury (C3:C4:C5:C6:C7:C8)		12:22:21:23:2:1

Results are displayed as mean ± standard deviation.

*ASIA Score: D, motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle grade of > 3. E: Normal motor and sensory function

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Table 2: Contact heat and dermatomal SSEP parameters

		Group			Significant pairwise comparisons‡
		Controls	[1]CSM_{above}	[2]$CSM_{at/below}$	
Contact heat evoked potentials					
C4 Dermatome					
	N2 Latency [ms]	363.9 ± 27.9	394.7 ± 40.5	400.7 ±61.8	Controls – CSM_{above} (p=0.002), Controls – $CSM_{at/below}$ (p=0.028)
	N2P2 Amplitude [µV]	24.5 ± 9.4	23.3 ± 13.7	21.0 ± 14.0	ns
	Pain rating (NRS)	5.7 ± 1.9	4.5 ± 2.5	4.3 ± 2.1	ns
C6 Dermatome					
	N2 Latency [ms]	386.8 ± 27.4	443.1 ± 44.0	423.7 ± 58.5	Controls – CSM_{above} (p=0.002), Controls – $CSM_{at/below}$ (p<0.001)
	N2P2 Amplitude [µV]	22.5 ± 6.9	14.8 ± 8.4	17.8 ± 8.9	Controls – CSM_{above} (p<0.007), Controls – $CSM_{at/below}$ (p=0.004)
	Pain rating (NRS)	4.9 ± 1.7	3.4 ± 2.4	4.3 ± 2.2	ns
C8 Dermatome					
	N2 Latency [ms]	404.6 ± 25.9	421.5 ± 38.5	428.5 ± 58.8	Controls – $CSM_{at/below}$ (p=0.023)
	N2P2 Amplitude [µV]	20.8 ± 6.9	20.1 ± 10.1	18.0 ± 8.4	Ns
	Pain rating (NRS)	4.5 ± 1.8	2.9 ± 2.8	3.7 ± 2.3	Ns
Dermatomal somatosensory evoked potentials					
C4 Dermatome	N1 Latency [ms]	14.3 ± 2.5*	14.7 ± 5.6	16.1 ± 3.2	ns
C6 Dermatome	N1 Latency [ms]	24.3 ± 2.4*	23.6 ± 8.2	28.1 ± 2.6	Controls – $CSM_{at/below}$ (p=0.041)
C8 Dermatome	N1 Latency [ms]	24.6 ± 2.1*	26.1 ± 9.2	27.1 ± 6.3	Controls – $CSM_{at/below}$ (p=0.039)

Results are displayed as mean ± standard deviation.

[1]**CSM_{above}**: Above the MRI level of lesion
[2]**$CSM_{at/below}$**: At/ below the MRI level of lesion

*: Reference values are taken from **Kramer et al., 2010**

‡: Bonferroni corrected

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Table 3: Clinical and demographic details of the longitudinal patients cohort

ID	Age	Gender	Time since injury [yrs]	Level of lesion	CHEPs Parameters at 1 year follow-up	MRI measures at 1 year follow-up	Progression of CSM
P01	35	F	2	C6/7	**Delayed N2 Latency and reduced N2P2 Amplitude**	**MCC and MSCC ↑, SCA ↓**	**Aggravation:** Clumsiness in hand
P02	41	F	3	C4	**Abolished CHEPs**	**MCC and MSCC ↑, SCA ↓**	**Aggravation:** Development of pain and paresthesia
P03	65	F	2	C5/6	**Abolished CHEPs**	**No change in MCC and MSCC, SCA ↓**	**Aggravation:** Development of pain, paresthesia, and incontinence
P04	69	M	4	C6/7	**Delayed N2 Latency and reduced N2P2 Amplitude**	**MCC and MSCC ↓, no change in SCA**	**Aggravation:** Development of pain, bladder problems
P05	57	M	3	C5/6	**No change in N2P2 amplitude and N2 Latency**	**MCC and MSCC ↑, no change in SCA**	**Stable:** No change in symptoms
P06	37	M	3	C5/6	**Abolished CHEPs**	**No change in MCC and MSCC, SCA ↓**	**Aggravation:** Gait disturbances
P07	32	M	2	C3/C4	**Abolished CHEPs**	**MCC and MSCC ↑, SCA ↓**	**Aggravation:** Development of pain and bladder problems, decline of sensory function
P08	60	M	3	C6	**Abolished CHEPs**	**No change in MCC, MSCC, and SCA**	**Aggravation:** Gait disturbances, clumsiness of hands, development of pain
P09	39	M	3	C6/7	**No change in N2P2 amplitude and N2 Latency**	**MCC and MSCC ↓**	**Stable:** No change in symptoms
P10	32	M	2	C6	**Delayed N2 Latency**	**MCC and MSCC ↓, no change in SCA**	**Aggravation:** Muscle weakness in both hands, incontinence
P11	51	M	4	C5/6	**Delayed N2 Latency and reduced N2P2 Amplitude**	**MCC and MSCC ↓, SCA ↓**	**Aggravation:** Development of pain
P12	62	M	3	**C5**	**No change in N2P2 amplitude and N2 Latency**	**MCC and MSCC ↑, SCA ↓**	**Stable:** No change in symptoms
P13	38	M	2	C5	**Delayed N2 Latency**	**No change in MCC and MSCC, no change in SCA**	**Aggravation:** Gait disturbances, clumsiness of hands, development of pain

MCC: Maximal Canal Compression
MSCC: Maximal Spinal Cord Compression
SCA: Spinal Cord Area